Long-term outcomes of His bundle pacing in patients with heart failure with left bundle branch block

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ABSTRACT
Objectives His bundle pacing (HBP) can potentially correct left bundle branch block (LBBB). We aimed to assess the efficacy of HBP to correct LBBB and long-term clinical outcomes with HBP in patients with heart failure (HF).

Methods This is an observational study of patients with HF with typical LBBB who were indicated for pacing therapy and were consecutively enrolled from one centre. Permanent HBP leads were implanted if the LBBB correction threshold was <3.5V/0.5 ms or 3.0 V/1.0 ms. Pacing parameters, left ventricular ejection fraction (LVEF), left ventricular end-systolic volume (LVESV) and New York Heart Association (NYHA) Class were assessed during follow-up.

Results In 74 enrolled patients (69.6±9.2 years and 43 men), LBBB correction was acutely achieved in 72 (97.3%) patients, and 56 (75.7%) patients received permanent HBP (pHBP) while 18 patients did not receive permanent HBP (non-permanent HBP), due to no LBBB correction (n=2), high LBBB correction thresholds (n=10) and fixation failure (n=6). The median follow-up period of pHBP was 37.1 (range 15.0–48.7) months. Thirty patients with pHBP had completed 3-year follow-up, with LVEF increased from baseline 32.4±8.9% to 55.9±10.7% (p<0.001), LVESV decreased from a baseline of 137.9±64.1 mL to 52.4±32.6 mL (p<0.001) and NYHA Class improvement from baseline 2.73±0.58 to 1.03±0.18 (p<0.001). LBBB correction threshold remained stable with acute threshold of 2.13±1.19V/0.5 ms to 2.29±0.92V/0.5 ms at 3-year follow-up (p>0.05).

Conclusions pHBP improved LVEF, LVESV and NYHA Class in patients with HF with typical LBBB.

INTRODUCTION
His bundle pacing (HBP) engages the His bundle–Purkinje conduction system and can result in physiological activation of the ventricles. In 2000, Deshmukh et al pioneered permanent HBP in 12 patients with heart failure who had atrial fibrillation and dilated cardiomyopathy and found improvements in left ventricle (LV) dimensions and cardiac function after HBP and atioventricular (AV) node ablation.1 Subsequently, a series of studies reported the feasibility and clinical benefits of HBP in patients with heart failure, AV node ablation for refractory atrial fibrillation, non-responders to cardiac resynchronisation therapy (CRT) and pacemaker-dependant patients.1–8

Most HBP clinical studies were conducted in patients with intact His–Purkinje conduction system. Clinically, patients with heart failure often have impaired His–Purkinje conduction, frequently manifested as left bundle branch block (LBBB). Early studies found LBBB could be corrected by HBP via electrode catheters in animals and humans.9 10 Lustgarten et al reported improvement with HBP similar to biventricular (BiV) pacing in patients with heart failure with LBBB.4 Recently, a feasibility study by Aijjola et al showed improvement in clinical and echocardiographic measures with HBP with up to 1-year follow-up in a small number of CRT patients.6 However, studies of LBBB correction by HBP are limited by small size and short follow-up. Furthermore, high pacing thresholds for correction of LBBB have dampened enthusiasm and created concerns about the implementation of HBP. The objective of this study was to explore the feasibility and characteristics of LBBB correction by HBP and evaluate clinical outcomes of permanent HBP in patients with heart failure.

METHODS
The present study was a single-centre prospective registry in patients with cardiac dysfunction and LBBB.

Study patients
Patients who met the inclusion criteria were enrolled between January 2012 and June 2017. The inclusion criteria should meet the following: (1) an ECG showed a wide QRS complex (>130 ms) and the morphology of typical complete LBBB,11 (2) patients had heart failure with New York Heart Association (NYHA) Class II–IV symptoms, (3) patients were indicated for CRT or pacing therapy, and (4) patients were at least 18 years old and not pregnant. Patients with any one of the following conditions were excluded: (1) non-specific intraventricular conduction delay or right bundle branch block, (2) patients expected with life expectancy less than 12 months and (3) patients declining guideline-indicated pacing therapy.

Implantation procedure and device programme
Implantation of the His bundle pacing lead was attempted in all enrolled patients and the technical method has been described.7 12 Briefly, after a ventricle back-up pacing lead was placed, the delivery sheath (model C315, seldomly and/or C304; Medtronic, Minneapolis, Minnesota, USA)
was inserted into the His bundle region in the AV septum. The Select Secure lead (model 3830; Medtronic) was advanced through the sheath for unipolar pacing during the implantation procedure. While the HBP had a high LBBB correction threshold or fixation failure after multiple attempts and positions, a second Select Secure system set was used and moved slightly distal to the location of the first lead to identify another region for HBP. An intracardiac electrogram from the lead tip electrode was recorded along with a 12-lead surface ECG (GE CardioLab EP Recording System 2000; GE, Milwaukee, Wisconsin, USA). Once pacing parameters were acceptable (LBBB correction threshold ≤3.5 V/0.5 ms or 3.0 V/1.0 ms), the Select Secure pacing lead was fixed into the His bundle region. The second lead, if used, was then repositioned in the right atrium or right ventricle (RV) position as indicated.

The criteria for HBP were used as described in the Recommendations of the Collaborative Working Group.\(^\text{13}\) Successful correction of LBBB was defined by paced ECG morphology without LBBB manifestation. Detailed information of lead connection to device is shown in online supplementary table 1. When HBP lead was connected to RV or LV port, the paced AV delay and longest interventricular (VV) interval was programmed to ensure HBP first and AV synchronisation. The pacing output for the LV or RV lead was programmed for ‘no effective pacing’ (eg, programmed to a minimum output or output off if possible), if there was no need of back-up pacing. In some patients, especially in those with high degree of AV block, we programmed RV or LV pacing as back-up pacing. When His pacing lead was connected to atrial port, standard AV interval and the shortest blanking period were programmed, safety ventricular pacing mode was off and optimal VV interval was programmed. In 18 patients who did not receive permanent HBP, 10 received CRT-D, 5 CRT-P and 3 dual-chamber pacemakers.

### Data collection and follow-up

The baseline demographic and medical history was collected at enrolment. Postimplantation clinical assessments, including echocardiography, NYHA functional class and blood B-type natriuretic peptide (BNP) concentration, were collected at 3–6 months and annually. Echocardiographic images were obtained in the standard parasternal long-axis and short-axis and apical four-chamber and two-chamber views using commercially available ultrasound equipment (Philips, IE Elite, USA). Left ventricular ejection fraction (LVEF) and LV end-systolic volume (LVESV) were measured. Mitral and tricuspid valve regurgitation were graded (severity level 0–3) by the proportion of jet area as a percentage of left/right atrial area. Lead electrical data were collected at outpatient visits at 3 months, 6 months and annually. Lead and implantation-related complications such as infection, dislodgement, loss of capture and early battery depletion were tracked during device follow-up visits.

### Statistical analyses

Continuous variables were expressed as mean±SD or median (first quartile, third quartile). Independent two-samples t-tests were performed to compare the differences between the two groups, and paired t-test was used to compare the differences between two time points within the same group during the follow-up if they met normal distribution. Otherwise, Mann-Whitney U test between-group comparisons or Wilcoxon signed-rank test within-group comparisons were used to assess the aforementioned differences. Categorical data were described as number (%) and \(\chi^2\) test or Fisher’s exact test (if the sample size is less than 40 or the minimum theoretical frequency is less than 1) was used to examine the aforementioned differences. The data managements and analyses were applied with SPSS V.20.0. All tests were two-sided and \(p\leq0.05\) was set up as the statistically significant level.

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**Figure 1** Flowchart of patients. HBP, His bundle pacing; LBBB, left bundle branch block; PM, pacemaker; BVP, biventricular pacing.
RESULTS

Implantation results and patient characteristics

His bundle capture was achieved in all 74 enrolled patients and LBBB was correctable by HBP in 72 patients (97.3%, figure 1). After acute HBP, 56 patients (75.7%) of all enrolled patients received permanent HBP (pHBP) and the remaining 18 patients did not receive permanent HBP (non-permanent HBP, npHBP) due to either failure to correct the LBBB by HBP (n=2), high correction threshold (>3.5 V/0.5 ms and >3.0 V/1.0 ms, n=10) or fixation failure (n=6). Patient clinical characteristics are summarised in table 1. Of note, most enrolled patients (n=61, 82.4%) had an LVEF ≤40% (HFpEF) while the remaining 13 patients (17.6%) had an LVEF >40% (HFrEF). There was no significant difference in patients’ baseline characteristics between patients with pHBP versus those with npHBP in table 1.

His bundle pacing at implantation

The overall ECG QRSd was 170.9±17.9 ms during intrinsic rhythm and 113.8±24.1 ms after LBBB correction by HBP (p<0.001). As shown in table 2, 55 of 72 patients had selective HBP (SHBP) and 17 patients had non-selective HBE. In patients who did not receive pHBP, the ECG QRSd was 174.6±12.1 ms during intrinsic rhythm, 103.5±17.1 ms during acute SHBP and 129.9±12.3 ms during BiV pacing (p<0.001 between SHBP and BiV pacing). Atrophicventricular block (AVB) relative to the procedure occurred in 34 patients and recovered in 23. In 56 patients with pHBP, the overall average His capture threshold was 0.86±0.55 V and the LBBB correction threshold was 1.89±1.12 V. Forty-four patients had higher LBBB correction threshold (2.13±1.1 V/0.5 ms) than His capture threshold (0.82±0.52 V/0.5 ms, figure 2), 12 patients had same His capture threshold and LBBB correction threshold (0.80±0.31 V/0.5 ms, figure 3). R wave amplitude was 3.6±2.2 mV and pacing impedance was 503.8±67.6 Ω.

Device HBP performance during follow-up

His capture and LBBB correction threshold are shown in figure 4. In 30 patients who completed 3-year follow-up, the His capture thresholds were 0.97±0.63 mV/0.5 ms at baseline and 1.28±0.69 mV/0.5 ms at 3-year follow-up (p=0.006) and LBBB correction thresholds were 2.13±1.19 mV/0.5 ms at baseline and 2.29±0.92 mV/0.5 ms at 3-year follow-up (p=0.473). Five patients of 44 patients who had higher LBBB correction threshold than that of His capture experienced an increase in LBBB correction threshold by an absolute value of >1 V during 1-year follow-up and the maximum increase was 0.5 V/0.5 ms in 12 patients who had same His capture and LBBB correction threshold. The pacing proportion of HBP were 99.6±0.7% immediately after implantation, 99.6±1.1% at 1 year and 99.6±1.2% at 2 years.

Long-term improvement in echocardiographic measurements and clinical outcomes in patients with pHBP

Patients with pHBP had a median follow-up of 37 months. As shown in figure 5, 30 patients completed 3-year follow-up, with LVEF from a baseline of 32.4±8.9% to 55.9±10.7% (p<0.001), LVESV from a baseline of 137.9±64.1 mL to 52.4±32.6 mL (p<0.001) and NYHA Class from a baseline of 2.73±0.58 to 1.03±0.18 (p<0.001). At 1-year follow-up, 88.9% patients who had an LVEF ≤40% had their LVEF improve to more than 50% over baseline. The magnitude of improvement in LVEF was significantly greater in patients with lower baseline LVEF (online supplementary figure 1). Other significant improvements at 1 year of HBP included BNP, NYHA classification, cardiothoracic ratio and left atrial dimension, and the severity of mitral and tricuspid valve regurgitation is shown in table 3.

Follow-up outcomes in patients with BiV pacing

Of 18 patients who did not receive permanent HBP, 15 patients received BiV pacing, of whom 12 patients completed at least...
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Figure 2  Left bundle branch block (LBBB) correction by His bundle pacing (HBP) in a patient. (A) 12-lead ECG and intracardiac electrogram recorded by His pacing lead. (A1) Intrinsic rhythm. (A2) His bundle pacing at 0.8 V/0.5 ms with His capture. (A3) His bundle pacing at 1.5 V/0.5 ms with LBBB correction. (B) Chest X-ray immediately before HBP (left, with enlarged cardiac silhouette) and after 3 years (right, with a reduced cardiac silhouette) after the implantation. (C) Schematic representations of activation conduction with C1–C3 corresponding to A1–A3. HB, His bundle; LBB, left bundle branch; LV, left ventricle; RBB, right bundle branch; RV, right ventricle.

Clinical events during follow-up

During the follow-up period, three patients with pHBP died (one sudden death at 1 month, one with pulmonary embolism at 10 months and another due to end-stage cancer at 16 months), one had device replacement at 18 months due to battery depletion and the pacing mode was programmed to BiV pacing, and one device extraction due to breast cancer and pocket skin infection at 10 months. There were no implantation-related complications such as lead dislodgement and exit block during follow-up. Two patients with npHBP died (one due to end-stage heart failure at 12 months and the other one with unknown cause within 1 month).

DISCUSSION

Fibres of conduction fascicles are present in the His bundle and are predestined for the left or right bundle branches either proximally or distally.\textsuperscript{14,15} The study by El-Sherif et al indicated that block could occur in the proximal His bundle with LBBB and pacing from the distal HBP could normalise bundle branch block.\textsuperscript{9} Later, patient studies demonstrated the feasibility of LBBB correction by HBP.\textsuperscript{4,6,16,17} The present study also demonstrated LBBB correction by HBP.

Clinical findings in the present study were consistent with those observed from prior studies in patients with heart failure with bundle branch block.\textsuperscript{4,6,17} However, the present study has the largest number of patients with typical LBBB and HBP and a longer follow-up (median 37 months) compared with previous studies.\textsuperscript{4,6,16} Furthermore, the magnitude of improvement we observed was greater than that in previous studies,\textsuperscript{4,6} which is likely related to greater narrowing of QRS duration, longer follow-up and different patient characteristics (eg, more patients with non-ischaemic cardiomyopathy and all patients with typical LBBB).

Most of our enrolled patients who received permanent HBP were CRT-indicated and the improvement in clinical outcome and echocardiographic measurements was dramatic with 89% of patients having over 50% improvement of LVEF at 1-year follow-up, which is greater than the percentage of CRT super-responders reported in literature.\textsuperscript{18,19} There was no significant difference in echocardiographic clinical outcomes between patients with permanent HBP and those with BiV pacing. However, due to small numbers and the non-randomised study design, further investigations should look at whether HBP can be an alternative to conventional CRT.\textsuperscript{17,20,21}

Compared with previous studies in which high pacing output was needed to correct LBBB,\textsuperscript{4,6,16,17} we found in 21.4% studied patients that HBP at the capture threshold could correct LBBB with a low pacing threshold, likely because the pacing site is near or beyond the region of block, as we reported previously.\textsuperscript{22} This finding is important for reducing the risk of exit block due to progression of distal conduction system disease and allowed us to use low pacing outputs to restore His–Purkinje conduction. The present study showed a high occurrence of AV block during lead placement, which implies the lead may have injured the right
Figure 3  Left bundle branch block (LBBB) correction by pacing at the distal His bundle in a patient. (A) 12-lead ECG and intracardiac electrogram. (A1) Intrinsic rhythm. (A2) His bundle pacing at 6 V/0.5 ms for LBBB correction at proximal His bundle (His P). (A3) Escape rhythm with complete AV block caused by the procedure adding a second lead (His D, site 2) using the dual-lead method. Of note, His potentials were recorded at proximal His bundle lead, not in distal His bundle lead. (A4) His D pacing could correct LBBB at His capture threshold (0.5 V/0.5 ms) and did not capture the His potential in His P lead. (B) Fluoroscopic imaging showing dual leads with one lead (site 1) for His P and the second lead (site 2) for His D. (C) Schematic representations of activation conduction with C2–C4 corresponding to A2–A4. HB, His bundle; LBB, left bundle branch; LV, left ventricle; RBB, right bundle branch; RV, right ventricle.

Figure 4  Pacing outputs for capturing His bundle and left bundle branch block (LBBB) correction at baseline (blue) and during follow-up (orange). (A) His capture threshold; (B) LBBB correction threshold. Mean value±SD was inserted in the bar with p value for the comparison between baseline and follow-up values. Numbers at the bottom represent measured numbers over the expected patient numbers. 3M, 3 months; 6M, 6 months; 1Y, 1 year; 2Y, 2 years; 3Y, 3 years of follow-up.

bundle branch. The dual-lead method used in the present study facilitated placing the His lead at or near the distal His bundle.

The present study achieved a 97.3% success rate of LBBB correction by HBP at implantation, which was higher than that reported previously.4 6 17 The study showed a relatively stable LBBB correction threshold over long-term follow-up and no lead dislodgements or exit block, suggesting the feasibility of long-term HBP. However, improvement in implant tools and technique is needed to reduce or avoid traumatic AVB by HBP lead placement.

Limitation
This single-centre, one-arm, non-randomised study was designed as an initial step to assess the feasibility of LBBB correction by HBP and the long-term clinical outcomes of permanent HBP in patients with heart failure. Although the small sample size will lead to low power, the improvements in echocardiographic measurements and clinical cardiac function assessment are significant. HBP could narrow QRS duration more than bi-ventricular pacing; however, the question of whether clinical outcome with HBP is better than that by CRT should be answered with future multicentre randomised controlled studies.

Most patients (85.1%) in the present study had non-ischaeic cardiomyopathy while previous major CRT trials or similar studies of HBP had a majority of patients with ischaemic cardiomyopathy. Thus, the study cohort may not broadly represent the heart failure population, especially for patients in Western countries. Whether the high rate of response to HBP in the present study is related to the patient population needs further investigation.

Moreover, procedure and success rate of HBP implantation depend on individual implanters’ technical experience. Further investigation is warranted to standardise this procedure.
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Conclusions
In the present study, HBP could correct LBBB in most patients with heart failure with typical LBBB. Distinctive ECG phenomena during LBBB correction is associated with a pacing site near the proximal His bundle (higher pacing threshold for LBBB correction) or the distal His bundle (low pacing threshold for LBBB correction). During a median of 37 months of follow-up after permanent HBP, significant improvements in clinical assessments and echocardiographic measurements were observed. With further technical improvement in pacing delivery tools and leads and randomised clinical trials to compare HBP with other pacing therapies such as CRT, His bundle pacing may become an option for patients with LBBB who need pacing therapy.

Key questions
What is already known on this subject?
► Ventricular dyssynchrony caused by left bundle branch block (LBBB) is one cause of heart failure (HF). His bundle pacing can potentially be an alternative cardiac resynchronisation therapy (CRT) for patients with HF with LBBB and has recently been increasingly investigated.

What might this study add?
► LBBB was acutely correctable by His bundle pacing (HBP) in 97% of patients and long-term (median 37 months) significant improvements in clinical function and echocardiographic measurements were observed in patients who received permanent HBP.

► Additionally, the present study found two types of LBBB correction by HBP: (1) His bundle was captured at a low threshold and LBBB correction required a higher pacing output by the same pacing lead; (2) LBBB was corrected at the same threshold when His bundle was captured.

How might this impact on clinical practice?
► HBP could be considered if a patient with typical LBBB suffers from HF. However, randomised control trials of HBP versus CRT is needed in this patient group.

Table 3
Clinical and echocardiographic measurements at 1-year follow-up

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<th>HBP with HFrEF (n=36)</th>
<th>BIV pacing (n=12)</th>
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<tr>
<td>TR</td>
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<td>BNP (pg/mL)</td>
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<td>NYHA Class</td>
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*P<0.001 and **P<0.05, when compared with baseline.
†P values, comparison between change of baseline and 1-year follow-up in HBP and BIV pacing groups.

Contributors
Each author listed in the manuscript has contributed significantly to the submitted work. Conception and design: WH, LS. Analysis and interpretation of data: WH, SW, LW, GM. Drafting of the manuscript and revising it critically for important intellectual content: SW, FX, XZ, PV, KJ. Final approval of the manuscript submitted: WH, LS, SW. All authors approved the final version of the paper.

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Competing interests
XZ is an employee of Medtronic plc. PV and KAE are consultants, investigators and receive honoraria from Medtronic plc.

Patient consent
Obtained.

Ethics approval
The study protocol was approved by the Institutional Review Board of the First Affiliated Hospital of Wenzhou Medical University.

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